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Year: 2013

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## **Acute neurotoxicity associated with recreational use of methylmethaqualone confirmed by liquid chromatography tandem mass spectrometry**

Ceschi, A ; Giardelli, G ; Müller, D M ; Elavumkudy, S ; Manini, A F ; Rauber-Lüthy, C ; Hofer, K E

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DOI: <https://doi.org/10.3109/15563650.2012.758855>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-70550>

Journal Article

Accepted Version

Originally published at:

Ceschi, A; Giardelli, G; Müller, D M; Elavumkudy, S; Manini, A F; Rauber-Lüthy, C; Hofer, K E (2013). Acute neurotoxicity associated with recreational use of methylmethaqualone confirmed by liquid chromatography tandem mass spectrometry. *Clinical Toxicology*, 51(1):54-57.

DOI: <https://doi.org/10.3109/15563650.2012.758855>

# **Acute neurotoxicity associated with recreational use of methylnmethaqualone confirmed by liquid chromatography tandem mass spectrometry**

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The paper is written in **US English**

**Running head:** Acute neurotoxicity after methylnmethaqualone abuse.

**Keywords:**

drug of abuse, designer drug, methaqualone, acute toxicity.

**Number of references:** 20

**Figures:** 2

## **Abstract**

Methylmethaqualone is a sedative designer drug created by adding a methyl group to the 3-phenyl ring of methaqualone, and is at present not subject to restrictive regulation in many countries. To our knowledge, no case of methylmethaqualone abuse has been published to date in the scientific literature, and the only sources of information are users' reports on Web discussion forums and data from preclinical animal studies. We report a case of oral methylmethaqualone abuse confirmed by liquid chromatography tandem mass spectrometry in a 24-year-old previously healthy Caucasian male. Observed symptoms and signs such as central nervous system depression alternating with excitation, psychomotor agitation, muscle hyperactivity, and tachycardia were compatible with methaqualone-induced adverse effects. Except for the mild tachycardia (115 beats/min), other vital signs were normal: blood pressure 134/89 mmHg, body temperature 36.2°C (97.16°F), peripheral oxygen saturation 99% while breathing room air. The ECG showed no prolongation of the QT interval and the QRS duration was normal. Laboratory analysis revealed a slight increase in creatine kinase (368 U/L) and alanine aminotransferase (90 U/L) serum concentrations. Blood alcohol concentration was 0.32 g/L. Methylmethaqualone was identified in a serum sample collected on admission which was analyzed by a liquid chromatography tandem mass spectrometry toxicological screening method using turbulent flow online extraction. After a few days the patient ingested the same amount of substance with identical symptoms. Based on the chemical structure and animal data, and according to this case report and users' Web reports, methylmethaqualone appears to have a similar acute toxicity profile to methaqualone, with marked psychomotor stimulation. Symptoms of acute toxicity can be expected to resolve with supportive care.



## Introduction

Methylmethaqualone (MMQ), 3-(2,4-dimethylphenyl)-2-methylquinazolin-4(3H)-one, is a product of rational drug design, created by modifying the chemical structure of methaqualone by adding a methyl group to the 3-phenyl ring (Fig. 1) with the aim to avoid the provisions of existing drug laws but retaining psychoactive properties.<sup>1</sup> The parent compound methaqualone is a highly addictive quinazolinone derivative<sup>2</sup> with sedative-hypnotic, anticonvulsant, and anxiolytic properties via action on the GABA-A receptor.<sup>3</sup> Due to its extensive history of misuse, the drug has been pulled from multiple markets worldwide.<sup>4,5</sup> Other sedative quinazolinone derivatives such as mecloqualone, cloroqualone, and etaqualone were removed from the market due to concerns about their potential for abuse and overdose.<sup>5</sup> There are no reports in the accessible scientific literature on the human pharmacology, toxicology, and safety of MMQ.

The structural identification of MMQ by mass spectrometry and proton NMR spectroscopy in a confiscated sample has been previously described,<sup>1</sup> but established analytic methods in serum are lacking. As a consequence of structural similarity, the sedative-hypnotic effects of MMQ might be assumed to be similar to those of methaqualone, although the appearance of excitation and myoclonic states accompanying the hypnotic activity has been described for MMQ in animal studies.<sup>6</sup> Since, to our knowledge, no case of abuse of MMQ has been published in the literature, the only sources of information are illegal drug users' Web discussion forums, in which euphoria, relaxation, memory loss, CNS depression, muscular spasms, and seizures are mentioned in a dose-dependent manner.<sup>7</sup> A search of the US-based National Poison Database System (NPDS) between 2009-2010 retrieved no mentions of methylmethaqualone/MMQ.

MMQ is generally used in doses of 50 to 200 mg; 300 mg are reported to induce muscle twitching, muscular spasms, and prolonged sedation.<sup>7,8</sup> Effects are described to begin after 20 to 30 minutes, and to persist for 4 to 6 hours.<sup>7,8</sup> MMQ is usually ingested, although sublingual application and smoking of lower doses has rarely been reported.<sup>7,8</sup> We present a case of MMQ abuse confirmed by the identification of the substance in serum by liquid chromatography tandem mass spectrometry.

### **Case report**

A 24-year-old previously healthy Caucasian male was admitted to the emergency department (ED) of our hospital following the acute onset of severe psychomotor agitation. One hour before admission, the patient was found at home by his parents in a somnolent state which suddenly switched to severe psychomotor agitation with generalized clonic muscle contractions and urinary incontinence. Paramedics found the patient extremely agitated and confused, and administered 10 mg midazolam intravenously with subsequent improvement in agitation. The patient admitted to having ingested up to two 500 mg MMQ tablets (obtained from a friend who had bought them from a dealer) with wine that evening (approximately 2 - 3 hours before admission to the ED) for recreational purposes.

On arrival to the ED, the patient was intermittently confused but his agitation had resolved. Except for a mild tachycardia (115 beats/min), vital signs were normal (blood pressure 134/89 mmHg, body temperature 36.2°C (97.16°F), peripheral oxygen saturation 99% while breathing room air). The neurological examination revealed a mild generalized resting tremor of upper and lower limbs. The pupils were mydriatic (moderate dilatation of approximately 7 mm) with normal reaction to light.

No nystagmus was observed. The rest of the neurological examination and the general physical examination were unremarkable.

The ECG was normal, except for mild sinus tachycardia; there was no prolongation of the QT interval and the QRS duration was normal (89 ms). Laboratory analysis revealed a slight increase in creatine kinase (368 U/L; reference range 0 - 200 U/L) and alanine aminotransferase (90 U/L; reference range < 41 U/L) serum concentrations. Blood alcohol concentration was 0.32 g/L (the legal alcohol limit for drivers in the UK is 0.8 g/L). Other parameters, including serum electrolytes, creatinine, complete blood count, other liver function tests, and thyroid stimulating hormone level were within normal limits. Arterial blood gas analysis (room air) showed pH 7.418, pO<sub>2</sub> 11.5 kPa (86 mmHg), pCO<sub>2</sub> 5.07 kPa (38 mmHg), SatO<sub>2</sub> 97%, bicarbonate 24.1 mmol/L, and lactate concentration 2.0 mmol/L. ELISA urine toxicology screen was negative for benzodiazepines, cocaine, amphetamine, tetrahydro-cannabinol, opioids, barbiturates, methadone, TCAs, MDMA, and methamphetamines.

A serum sample collected on admission was analyzed by a liquid chromatography tandem mass spectrometry toxicological screening method using turbulent flow online extraction.<sup>9,10</sup> MMQ was identified by comparing the MS<sup>2</sup> and MS<sup>3</sup> spectra with the respective spectra of methaqualone, whose library spectra produced from a pure reference compound were available in the spectral library of the Institute for Clinical Chemistry, University Hospital Zurich.<sup>9</sup> Because of the additional methyl group, the mass-to-charge ratio of the protonated molecule [M+H]<sup>+</sup> of MMQ was increased by 14 amu ([M+H]<sup>+</sup> of methaqualone: *m/z* 251, [M+H]<sup>+</sup> of MMQ: *m/z* 265). Depending on which part of the molecule the fragments of MMQ were derived from, they either had the same mass-to-charge ratio as the respective fragments of



methaqualone, or, if the fragment contained the moiety with the additional methyl group which MMQ has compared with methaqualone, their mass-to-charge ratio was increased by 14 amu (Fig. 2).

Using the same liquid chromatography tandem mass spectrometry screening method, a search for a wide variety of medications and drugs of abuse (more than 900 substances) was performed (general unknown screening). Besides midazolam (which was administered by prehospital emergency services), no other substances were identified.

The patient was admitted to the medical ward for observation. The subsequent clinical course was uneventful and he was therefore discharged home on the following day.

Ten days later the patient presented identical symptoms and signs after a repeated ingestion of the same amount of MMQ tablets. The response to 15 mg midazolam administered intramuscularly by paramedics was favourable. ELISA urine toxicology screen was negative. Blood alcohol concentration was < 0.05 g/L and creatine kinase 225 U/L. After initial evaluation in the ED and following 2 hours uneventful observation, the patient was discharged home with the recommendation to consult a psychiatrist.

## **Discussion**

Recent years have been characterised by a dramatic increase in the production and sale, mainly through the Internet, of designer drugs with primarily stimulant, entactogenic, and hallucinogenic properties,<sup>11</sup> although designer sedatives such as MMQ and mebroqualone are also available on the market.<sup>1,8</sup> Designer drugs can have highly similar chemical structures to existing illegal drugs of abuse, in order to

elude existing regulations but to retain psychoactive properties of the parent compound.<sup>12</sup> Actually, MMQ is the methylated analogue, but not a metabolite,<sup>13</sup> of methaqualone, which is a quinazoline compound related functionally and structurally to glutethimide and the barbiturates.<sup>14</sup> The numerous cases of abuse of methaqualone reported soon after its introduction to the market, indicated a marked addictive potential of this substance which was also causing a severe withdrawal syndrome similar to delirium tremens characteristic of the sedative-hypnotic type of dependence.<sup>15</sup> Methaqualone was therefore withdrawn from the market in many developed countries in the early 1980s, and was listed in the UK as a class B drug under the Misuse of Drugs Act 1971 and classified as a Schedule I drug in the US in 1984. In contrast, to our knowledge, MMQ is at present not subject to restrictive regulations in many countries, especially those having no general analogue act or equivalent legislation.

Methaqualone overdose usually causes ataxia, lethargy, and CNS depression, although limb hyperreflexia, myoclonia, seizures, coma and other non-neurological symptoms such as respiratory and cardiac failure have been described after severe poisoning.<sup>14,16</sup> Psychomotor agitation was observed in a life-threatening intoxication,<sup>17</sup> and, at lower doses, recreational users have reported a euphoriant effect.<sup>18</sup>

MMQ users describe similar effects to those of methaqualone, and the symptoms and signs observed in our patient (CNS depression followed by psychomotor agitation, muscle hyperactivity, and tachycardia) are compatible with methaqualone-induced adverse effects. Furthermore, muscle hyperactivity presenting as muscle twitching or muscular spasms described as similar to GHB-induced seizures, is mentioned as undesirable effect in anecdotal reports of MMQ users,<sup>7</sup> and was also

observed in our patient. Moreover, animal studies have shown that MMQ can produce excitation and myoclonic states at doses only slightly above the effective sedative dose.<sup>6</sup> The initial neurological presentation of our patient is also compatible with an epileptic seizure, which has been reported after abuse of both MMQ<sup>7</sup> and methaqualone.<sup>17</sup>

A common dose of methaqualone for recreational use is reported to be 300 mg.<sup>19</sup> However, tolerance develops rapidly and some users may take up to 1000 - 2000 mg per day.<sup>20</sup> Users' reports discuss a higher potency of MMQ compared to methaqualone, and recommend doses of 50 - 200 mg of the former for recreational use.<sup>7,8</sup> However, in an animal study, mice required higher doses of MMQ compared to methaqualone to achieve a hypnotic effect.<sup>6</sup> In our case, 500 - 1000 mg of substance were ingested in the form of tablets and not as pure powder, therefore the effective ingested dose of MMQ might have been overestimated due to the possible presence of adulterants (e.g. starch, mannitol, inositol).

As a methaqualone-derivative, MMQ is likely addictive and therefore has potential for abuse but, at present, is not subject to restrictive regulations in many countries. Thus it seems plausible that the illicit use of this substance might increase internationally. For this reason, further studies are needed to determine the pharmacological and toxicological properties of MMQ, and to analyze patterns of acute toxicity in humans and its possible long-term effects, including dependency and withdrawal.

In conclusion, MMQ appears to have a similar acute toxicity profile to methaqualone, with marked psychomotor stimulation. Symptoms of acute toxicity can be expected to resolve within hours with supportive care.

**Patient's consent**

A document showing the patient's written consent to this publication is available on demand.

**Acknowledgements**

We thank Dr. Hugo Kupferschmidt, Swiss Toxicological Information Centre, for valuable discussions during the preparation of the manuscript, and Ms. Rose-Marie Hauser-Panagl for secretarial assistance.

**Declaration of interest**

None of the authors has conflicts of interest concerning commercial or financial involvements. No author is affiliated with an organization whose financial interests may be affected by material in the manuscript.

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